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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/678,997	10/04/2000	Michael David Bentley	34848/194868	4896

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EXAMINER

STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 05/31/2002

67

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/678,997

Applicant(s)

BENTLEY ET AL.

Examiner

Teresa E Strzelecka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 March 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 30-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 30-50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. This Office action is in response to an amendment filed on March 5, 2002. The Information Disclosure Statement received on May 13, 2002 has been considered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 30-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 30, 49 and 50 contain a limitation "...substantially hydrophilic conjugate...". It is not clear what degree of hydrophilicity is considered "substantial", especially since the only guidance provided by the specification is that "...By the term "substantially hydrophilic" it is intended to mean that the conjugate of this invention does not contain a substantially lipophilic moiety..." (page 5, lines 20-25), without definition of what "substantially lipophilic means.

B) Claim 33 contains a limitation "...said nonpeptidic polymer and said peptide are conjugated from solution". It is unclear what conjugation process is described by this limitation.

C) Claim 35 contains a limitation "...conjugate ... further characterized by conjugation of the peptide at least one terminus thereof." It is unclear what in the peptide is being conjugated.

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D) Claim 36 contains a limitation "...conjugate ... further characterized by conjugation of the peptide at least one N-terminus thereof". It is unclear what in the peptide is being conjugated. In addition, period at the end of this sentence is missing.

E) Claims 49 and 50 contain a limitation "...peptide covalently linked from solution...". It is unclear what conjugation process is described by this limitation.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 49 is rejected under 35 U.S.C. 102(b) as being anticipated by Poduslo et al. (U.S. Patent No. 5,670,477).

Poduslo et al. teach conjugates of neurologically active compounds which enhance their ability to cross the blood-brain barrier (BBB). The conjugate comprises a hydrophilic polyamine conjugated to a neurologically active compound, which may be epinephrine, norepinephrine, enkephalins, dynorphin, etc. (Abstract; col. 1, lines 47-61; col 4, lines 31-33; col. 6, lines 1-13; col. 7, lines 20-23). The polyamines (putrescine, spermine, spermidine, etc.) are covalently attached to the neurologically active compounds via ϵ -amino groups of lysines or γ -carboxyl groups of glutamates, or via numerous functional coupling groups (col. 15, lines 20-34, 54-65; col. 16, lines 38-67; col. 17, lines 1-57).

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Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 30-36, 45 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poduslo et al. (U.S. Patent No. 5,670,477), Hruby et al. (U.S. Patent No. 4,518,711) and Rodbard et al. (U.S. Patent No. 4,468,383).

A) Claim 30 is drawn to a substantially hydrophilic conjugate of an analgesic peptide, selected from the group consisting of biphalin and [D-Pen2, D-Pen5] enkephalin, with a water soluble, non-peptidic polymer, the conjugate being transportable across the BBB. Claim 31 is drawn to the conjugate having extended analgesic effect, claim 32 is drawn to the absence of lipophilic groups in the conjugate, and claim 33 is drawn to peptide and the polymer conjugated from solution. Claim 34 is drawn to the absence of non-covalent bonds in the conjugate, claims 35 and 36 are drawn to the conjugation of at least one peptide terminus. Claim 45 is drawn to a pharmaceutical composition comprising the conjugate. Claim 50 is drawn to a substantially hydrophilic conjugate of an analgesic peptide, selected from the group consisting of biphalin and [D-Pen2, D-Pen5] enkephalin, with a water soluble, non-peptidic polymer, the conjugate being transportable across the BBB, no non-covalent bonds and no lipophilic moieties.

B) Teachings of Poduslo et al. are described above. Poduslo et al. teach modification of enkephalins, but do not specifically teach biphalin (dimeric enkephalin) or [D-Pen2, D-Pen5] enkephalin.

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C) Hruby et al. teaches enkephalin analogs, [D-Pen2, D-Pen5] enkephalin among them, with analgesic activity (col. 5, lines 2-21). Rodbard et al. teach dimeric enkephalin molecules with analgesic effects (Abstract; col. 1, lines 20-40).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the conjugation method of Poduslo et al. applied to [D-Pen2, D-Pen5] enkephalin of Hruby et al. or biphalin of Rodbard et al. The motivation to do so, expressly provided by Hruby et al. and Rodbard et al., would have been that [D-Pen2, D-Pen5] enkephalin bound with enhanced specificity to the delta receptor and biphalin had higher affinity, association rate and specificity for the opiate receptor binding sites.

8. Claims 37-40, 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poduslo et al. (U.S. Patent No. 5,670,477), Hruby et al. (U.S. Patent No. 4,518,711) and Rodbard et al. (U.S. Patent No. 4,468,383) as applied to claim 30 above, and further in view of Harris et al. (U.S. Patent No. 5,932,462).

A) Claim 37 is drawn to the polymer being polyethylene glycol or a copolymer of polyethylene glycol and polypropylene glycol, claim 38 is drawn to the polymer being polyethylene glycol, claim 39 is drawn to different types of polyethylene glycol, claim 40 is drawn to the peptide being conjugated to at least one polyethylene glycol molecule. Claim 42 is drawn to the polyethylene glycol with average MW between 200 and 100,000 daltons, claim 43 is drawn to the polyethylene glycol with average MW between 1000 and 40,000 daltons, and claim 44 is drawn to the polyethylene glycol with average MW of 2000 daltons.

B) The teachings of Poduslo et al., Hruby et al. and Rodbard et al. are described above.

They do not teach conjugates with polyethylene glycol.

C) Harris et al. teaches branched, multi-armed polymers of polyethylene glycol, designed for modification of proteins (Abstract; col. 7, lines 33-67; col. 8, 9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have substituted the polyamines of Poduslo et al. in the conjugates with peptides of Hruby et al. and Rodbard et al. with polyethylene glycol molecules of Harris et al. The motivation to do so, expressly provided by Harris et al., would have been that proteins modified with polyethylene glycol retained their activity or had enhanced activity.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization

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where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
May 28, 2002

Kenneth R. Horlick
KENNETH R. HORLICK, PH.D.
PRIMARY EXAMINER

5/28/02